REMARKS/ARGUMENTS

Claims 5-8, 28, 35-37, 43-57 are pending in the Application. Claims 5, 6, 8, 28, 35, 36 and 49 have been amended herein. Claims 9-27, 29-34 and 38 are directed to embodiments of the present invention that do not fall within the Examiner's group selected by Applicants in response to the restriction requirement imposed by the Examiner as part of Paper No. 10. For this reason, Claims 9-27, 29-34 and 38 have been cancelled without intending to dedicate any patentable material to the public.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected Claims 5-8, 28, 35-37 and 43-57 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and use the invention. The Examiner argues that the specification does not show that any of the compounds falling within the scope of Claim 5 can be used to promote apoptosis, inhibit apoptosis or to alter any cellular function.

The Examiner correctly refers to page 13, line 3 of the specification as the starting point of the detailed description of the compounds of the present invention. This description continues through page 19, line 11 of the specification. Within that description, the structures of analogs of LPA, noted to be encompassed within the term "LPA" as used in the instant disclosure, are defined at page 13, line 23 through page 19, line 4. The Examiner contends that "LPA" is limited to C_{18} mono-unsaturated olefins. However, the reference on page 9, lines 27-28 notes that this reference is for the purposes of the figure legends only and that it does not specify a particular analog. Regardless, the definition of "LPA" for the purposes of the specification encompasses fatty acid esters other than C_{18} fatty acids (see, for example, page 13, lines 12-18) including those fatty acids

esterified through esters, reverse esters, and reverse thioesters (see page 18, lines 11-14). Thus the examples referred to below include the preparation and comparison of esters, reverse esters and thioesters.

Methods of procuring and isolating these compounds are described at page 19, line 11 through page 21, line 25. Detailed methods of making these analogs are described in Example 1 at page 47, line 8 through page 70, line 17. Applicants note that the synthesis of compounds 78, 48, 66 and 80 is described in detail at pages 69, 61, 65 and 69 of the specification, respectively, and that these compounds are within the presently pending claims. Thus, the instant specification provides detailed descriptions of methods of procuring and synthesizing LPA analogs encompassed by the presently pending claims such that one of skill in the art could make the compounds.

Example 2 describes the method of testing the anti-apoptotic activity of the compounds of the present invention at page 70, line 17 through page 71, line 14. Example 4 describes the testing of LPA and the analogs thereof encompassed within the presently pending claims at page 72, line 28 through page 77, line 12. The activity exhibited by these compounds relative to the effect of 18:1 LPA (itself defined within the specification at page 13, lines 8-15) is provided in Table 3 at page 73, line 21. As noted in Example 4 at page 77, lines 8-12, most of the LPA analogs tested exhibited anti-apoptotic activity comparable to lysophosphatidic acid while the phosphothionate analogs encompassed by Claim 5 showed significantly higher anti-apoptotic activity than lysophosphatidic acid. Thus, as shown in Table 3, compounds 78, 48, 66 and 80 show 160%, 130%, 130%, and 100% of the activity of the anti-apoptotic activity of 18:1 LPA respectively at lower concentrations. Therefore, the instant disclosure provides detailed descriptions of methods of using and comparing the compounds of the presently pending claims such that one of skill in the art could use compounds.

In view of the foregoing remarks, applicants submit that one of skill in the art could learn to make and use the presently claimed invention by reference to the instant specification and there is adequate enablement in the specification for Claims 5-8, 28- 35-37 and 43-57. Therefore, Applicants respectively request the Examiner's rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claims 6, 8, 28, 35 and 52 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner notes that Claim 6 encompasses salts of reverse ester LPA's. Applicant's have amended Claim 6 to remove the recitation of salts of either compound.

The Examiner argues that the term "treating apoptosis" as used in Claim 8, is indefinite. Applicants have amended Claim 8 to recite "inhibiting apoptosis" to avoid placing a value judgement on whether the interference with apoptosis would be considered to be "beneficial" in every instance. Support for this amendment is found at least at page 37, line 27 through page 38, line 28 of the specification.

The Examiner notes that Claim 28 appears to require a compound of Claim 5, a pharmaceutical excipient and at least one other, unspecified, moiety. Applicants have amended Claim 28 to correctly recite a compound of claim 5 and at least one pharmaceutical excipient.

The Examiner notes that Claim 35 lacks a process step. Claim 35 has been amended to properly recite a dispersion of a compound of Claim 5.

The Examiner states that Claim 52 is indefinite as to the manifestations of the preservation recited. However, Applicants note that the claim recites the preservation of a donor organ, not the

entire donor organism. Thus, the preservation is manifested as the viability or prolonged viability of an organ that has been harvested for donation to another organism. After harvest, donor organs rapidly deteriorate if not preserved until the time of transplant into the recipient organism. This preservation takes many forms including storage on ice, perfusion with different solutions and, in the case of Claim 52, injection with a compound of Claim 5. Therefore, applicants submit that Claim 52 is sufficiently definite to meet the requirements of 35 U.S.C. § 112, second paragraph.

Claim Rejections Under 35 U.S.C. § 102

The Examiner has maintained the rejection of Claim 5 under 35 U.S.C. § 102(b) as being anticipated by Helv Chimica Acta 41, 1163-68, 1958 (hereinafter "Cherbuliez"). The Examiner cites Compound 8 of Table III of Cherbuliez as anticipating Claim 5 when the substituents of Claim 5 are defined as W=OH, R=CH_2-CH_3, X=O, Z=hydrogen, Y=O, and W=Q (first occurrence) and argues that Applicant's previous response amending the definition of substituent L is irrelevant to the analysis of anticipation of Claim 5 by Cherbuliez.

Compound 8 of Table III on page 1167 of Cherbuliez is:

P-O-CH_2-CH_2-CH_2-COO-Et
γ β α

whereas, using the variables as defined by the Examiner (as well as n=0), the first occurrence of Q has the structure:

P-O-CH_2-CH_2-COO-Et
β α

In each case, the carbons between the carboxyl carbon and the phosphate are labeled as alpha, beta, etc., to the carboxyl carbon. With respect to Compound 8 of Cherbuliez, the molecule contains

three (3) carbons, alpha, beta, and gamma to the carboxyl group. In contrast, the molecule of Claim 5, as defined by the Examiner in reference to the first occurrence of Q has only two (2) carbons, alpha, and beta to the carboxyl group. Thus, the first occurrence of Q, as defined in Claim 5 cannot be anticipated by Compound 8 of Cherbuliez, regardless of the definitions of R, Z or n and this is the reason that Applicant's previous amendment of Claim 5 in response to the Examiner's citation of Cherbuliez assumed the second occurrence of Q.

The Examiner also cites Compound 8 of Cherbuliez as anticipating Claim 5 in the instance the substituent variables are defined as: W=OH, W= second occurrence of Q, R=CH_2CH_3, X=Y=L= oxygen, Z=hydrogen and m=zero. For the reasons described above, the second occurrence of Q cannot be anticipated by Compound 8 of Cherbuliez when m=zero. However, Applicants appreciate the Examiner's point that if m=1, V=H, and $(CH_2)_n$ and R together form CH_3CH_2-, then Compound 8 of Cherbuliez anticipates Claim 5. The Examiner also cites a compound in reactions 1 and 2 of J. Biol Chem 221:171-80 (1956) (hereinafter "Black"). The Examiner argues that Applicant's previous amendment to the definition of X is insufficient to alert one of skill in the art that the two occurrences of X in the formula must be the same molecule. Applicants have amended the definition of n to eliminate the instance in which $(CH_2)_n$ and R together can form methyl or ethyl within either occurrence of Q. That is, in each occurrence of Q, $(CH_2)_n$ and R together must be longer than ethyl. This distinguishes over all of the anticipating citations described above that were made by the Examiner or recognized by Applicants.

Applicants therefore submit that Claim 5, as amended, is not anticipated by Cherbuliez or Black and respectfully request the Examiner's rejections under 35 U.S.C. § 102(b) be withdrawn.

Based upon the foregoing, Applicants believe that all pending claims are in condition for allowance and such disposition is respectfully requested. In the event that a telephone conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

Respectfully submitted,

SHERIDAN ROSS P.C.

By: Robert D. Traver

Robert D. Traver
Registration No. 47,999
1560 Broadway, Suite 1200
Denver, Colorado 80202-5141
(303) 863-9700

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